Heartbreak: a model for depression

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Chapter 5

Brain reward responses associated to longitudinal changes in depressive symptoms after a romantic relationship breakup

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Abstract

The reward system has been suggested to be involved in (developing) clinical depression. By studying otherwise healthy people who suffer from a depression(-like) state following a negative event, possible alterations in reward-related processing can be detected at a subclinical level. We investigated whether processing of reward and punishment relates to depressive symptom trajectory following a romantic relationship breakup. Secondary, we investigated whether personality traits of rumination and neuroticism relate to processing of reward and punishment in our sample. To this end, women (n=48) who experienced a breakup performed a monetary incentive delay fMRI task. Cluster analysis revealed that individual depressive symptom trajectories following breakup could be clustered into four groups, labeled as: "resilience", "fast recovery", "slow recovery" and "chronic distress". Across our total sample, we performed three feature-based independent component analyses on the reward anticipation>baseline, punishment anticipation>baseline and reward anticipation>punishment anticipation contrast images to identify patterns of coactivated brain regions. Component loadings were compared between the groups and correlated with personality traits. The groups did not differ with regard to their loadings on any of the reward anticipation>baseline or punishment anticipation>baseline components. For the reward anticipation>baseline contrast, we revealed a negative correlation between component 1 (positive activation in occipital and parietal regions) and neuroticism. For the reward anticipation>punishment anticipation contrast, component 4 (frontal areas showing negative activation) was found to be more represented in the "chronic distress group" than in the "slow recovery group". Furthermore, we found a negative correlation between component 2 (occipital, parietal and frontal regions showing negative activation) and trait rumination. Taken together, our findings carefully point towards a relatedness of specific brain activation patterns, concerning the difference between reward anticipation and punishment anticipation, with the persistence of depressive symptoms over time and personality traits that are considered to be risk factors for depression.

5.1 Introduction

Studying depressive symptoms in nonclinical populations makes it possible to identify vulnerability factors for depression before it fully develops. Furthermore, contrary to clinical populations, the investigation of depressive symptoms in otherwise healthy individuals is not affected by influences of treatment and/or experiencing symptoms for already a long period of time. This could lead to a better understanding of the transition from healthy behavior, and corresponding brain activity, to depressive behavior and underlying mechanisms. It is known that the occurrence of a negative event can lead to the development of depressive symptoms (Kendler et al., 1999). For example, the breakup of a romantic relationship potentially leads to symptoms of depression. Previous research in our laboratory revealed elevated depressive symptom severity in individuals who experienced a romantic relationship breakup within the preceding six months compared to individuals in a romantic relationship (Verhallen et al., 2019). Additionally, we previously found that a substantial part of our sample suffered from symptoms of depression recent after breakup, which can last for several months (Chapter 4). Therefore, individuals suffering from breakup-related mood disturbances serve as an experimental human model to investigate depressive symptoms in otherwise healthy people and gain knowledge about vulnerability factors for developing (symptoms of) depression during a negative period in life.

Processes related to reward and punishment have been implicated in clinical depression. Anhedonia, a core symptom of depression, comprises reduced motivation and engagement in rewarding activities and absence of experiencing pleasure and joy (Rizvi et al., 2016). Depression has been suggested to be accompanied by decreased sensitivity for rewarding stimuli as well as an increased sensitivity for punishing stimuli, leading to a disbalance in reward processing and associated behavior (Kumar et al., 2018). This could underlie the cognitive bias towards negative stimuli as thought to be involved in depression (Roiser et al., 2012). For example, less striatal activity in response to monetary rewards (Takamura et al., 2017) and less deactivation of the amygdala during negative feedback (Taylor Tavares et al., 2008) was found in patients with depression compared to healthy controls. Notably, alterations have also been reported in undiagnosed individuals without depressive symptomatology,

but who were at a high familial risk for depression. For instance, female adolescents with a mother diagnosed with depression but without current or a history of depressive symptoms themselves displayed different patterns of brain activation (i.e., less activation of the putamen and left insula during reward anticipation and more activation of the anterior cingulate gyrus during punishment consumption), compared to female adolescents with a low familial risk of developing depression (Gotlib et al., 2010). In a study by Olino et al. (2014), high risk adolescents were found to have reduced striatal responses during anticipation of monetary reward. Sharp et al. (2014) showed that adolescents with current symptoms of depression as well as adolescents with a high familial risk for depression display less ventral striatal activation during reward consumption compared to healthy controls. In addition, Fisher et al. (2019) show specific brain patterns during reward anticipation (i.e., activation of the anterior cingulate cortex and putamen) that were able to differentiate between resilient at-risk individuals and at-risk individuals who previously have experienced a depressive episode. Furthermore, in that study, resilient at-risk individuals displayed greater activation in the middle frontal gyrus during reward anticipation and reduced activation in the superior frontal gyrus and cuneus during reward consumption compared to at-risk individuals with a history of depression (Fischer et al., 2019).

Additional to the relation between the reward system and depression, reward processing has been suggested to be related to specific personality traits that are considered to be risk factors for depression, such as rumination and neuroticism. Individuals scoring high on rumination tend to engage in repetitive negative thinking and this style of thinking is often seen in patients with depression (Huffziger et al., 2009; Nolen-Hoeksema, 1991; Nolen-Hoeksema, 2000). This observation suggests that the interplay between susceptibility of negative thinking and alterations in reward-related processing plays an important role in depressive symptomatology. High scores on neuroticism have also been linked to depression (Costa & McCrae, 1980). Neuroticism refers to difficulties in regulating negative emotions and higher emotional reactivity (Costa & McCrae, 1980; Servaas, van der Velde et al., 2013). In our previous study on the same sample, we observed higher neuroticism and trait rumination levels among individuals who reported prolonged distress after a breakup compared to individuals who recovered

throughout the study period or were never affected (Chapter 4). In previous studies, among both healthy individuals and patients with depression, rumination and neuroticism were found to be related to reward processing. Kocsel et al. (2017) found an association between trait rumination and the difference in brain activation between reward processing and punishment processing (i.e., activation in the anterior insula, inferior frontal gyrus and rolandic operculum) among healthy individuals. Furthermore, in individuals with a history of clinical depression, reduced activation in frontal areas of the brain during anticipating and consuming of punishment was found and punishment consumption was associated with higher levels of trait rumination (Schiller, Minkel, Smoski, & Dichter, 2013). In healthy individuals, a negative association was found between neuroticism level and amygdala activity as well as connectivity between the amygdala and, among others, the anterior cingulate cortex and insula in a reward learning task (Schweckendiek, Stark, & Klucken, 2016) and a similar result was found in a study by Klucken et al. (2019), but only in females.

Taken together, these findings suggest that reward-related brain responses play a role in depression, possibly mediated by personality traits and associated maladaptive thinking processes, and might serve as risk and protective factors for developing (symptoms of) depression.

In this chapter, we primarily aimed to investigate whether processing of reward and punishment relates to depressive symptom trajectory following romantic relationship breakup. Secondary, we aimed to investigate whether personality traits of rumination and neuroticism relate to processing of reward and punishment in our sample. Subjects performed a variant of the monetary incentive delay (MID) task, which is commonly used in fMRI studies to examine brain activity during anticipation and consumption of both reward and punishment (Knutson, Westdorp, Kaiser, & Hommer, 2000). As previous research in our laboratory revealed higher depression scores among women of the breakup group than among men (Verhallen et al., 2019), and depression rates are higher among women in the general population (Kessler et al., 1993), we included only women in the present study.

5.2 Methods

5.2.1 Experimental design

A longitudinal design was employed to examine depressive symptom severity during a period of 30 weeks following romantic relationship breakup. We included women who experienced a breakup within the preceding two months. Subjects visited our laboratory three times. During the third study visit subjects underwent an fMRI session, as we did not aim to investigate acute effects of the breakup. The fMRI session comprised in the following order: anatomical scan, resting-state run 1, MID task and resting-state run 2. Resting-state results will be presented elsewhere. An overview of the study visits and corresponding measurements can be found in Supplementary Figure 1.

Two subjects had their third study visit scheduled earlier than the study protocol anticipated. Two subjects dropped out during the study period. Two subjects decided not to undergo MRI scanning at the end of the study period, other measurements were obtained. Due to the COVID-19 pandemic and measures taken in the Netherlands, 36 subjects could not visit our laboratory for their third study visit (including MRI scans).

Written informed consent was obtained from all subjects during the first visit prior to conductance of any measurements. The study was approved by the Medical Ethical Committee of the University Medical Center Groningen (UMCG) and conducted in accordance with the principles of the Declaration of Helsinki. Subjects received a financial compensation of €75 after the last visit. Subjects who decided to withdraw from the study received financial compensation on a pro rata basis. The study was registered in The Netherlands National Trial Register (NTR), number 7365.

5.2.2 Subjects

Subjects were recruited via (social) media and by distributing flyers at the UMCG, the University of Groningen, the University of Applied Sciences and public places of the city of Groningen. After contacting the research team, a telephone intake was scheduled to explain study procedures and assess study eligibility.

Women who experienced a romantic relationship breakup within the preceding two months (at the time of written informed consent) with a relationship duration of at least six months were included in our study. Other inclusion criteria were: 1) age between 18 and 35 years 2) Caucasian ethnicity 3) right-handed 4) heterosexual 5) Dutch as a native language (all self-reported). Subjects who met any of the following criteria were not allowed to participate: 1) diagnosis of a neurological disorder 2) diagnosis of a psychiatric disorder 3) vision problems that could not be corrected adequately 4) not able to undergo 3 Tesla MRI scanning. MRI exclusion criteria include MRI incompatible implants or (metal) objects in the body, (suspected) pregnancy, claustrophobia and the refusal to be informed of brain abnormalities that could be detected serendipitously during the scan.

Three subjects were excluded after the first study visit; new information obtained at the first visit implied study ineligibility.

5.2.3 Data acquisition procedures

5.2.3.1 Questionnaires

We used the Major depression inventory (MDI) to examine depressive symptom severity (Bech et al., 2001). Subjects filled out the MDI every 14 days (+2 days/-1 day) during the study period, resulting in sixteen consecutive MDI scores for every subject. Subjects who had their MRI scan +2 weeks or more, filled out an additional MDI. As presented in Chapter 4 of this thesis, we described individual MDI trajectories and grouped our subjects according to their depressive symptom trajectory using K-means clustering for longitudinal data (Genolini & Falissard, 2011). To assess trait rumination and neuroticism levels, subjects filled out the RRS-NL-EXT (Schoofs, H. et al., 2010) and the NEO-FFI (Costa & McCrae, 1992), respectively.

5.2.3.2 Monetary incentive delay task

We used an in-house developed game-like monetary incentive delay (MID) task (Knutson et al., 2000). We used OpenSesame version 3.1.4 to present the task at the day of the experiment (Mathôt et al., 2012). The MID task is commonly used to assess processing of reward and punishment at the neural level

(Knutson et al., 2000). The task is able to distinguish between the anticipation phase and the consumption phase of reward-related processing. The MID task as used in our study consisted of three conditions; reward, punishment, and neutral. During the reward condition, subjects were instructed to try to earn (hypothetical) money by responding as fast as possible after appearance of a target stimulus (white square). When the subjects were able to respond before the target stimulus disappeared, they earned the pre-specified amount of money. Two levels of reward were used (low and high, +€0.50 and +€5 for low and high, respectively). During the punishment condition, subjects were instructed to try to avoid losing (hypothetical) money by responding as fast as possible after presentation of the target stimulus. Similar to the reward condition, two levels were used (low and high, -€0.50 and -€5 for low and high, respectively). After each trial, subjects received feedback (1500 ms) about the monetary outcome for that specific trial and the accumulated amount of money. The third condition (neutral) can be seen as a control condition in which subjects only have to respond before disappearance of the target stimulus without earning or losing money. We implemented an in-house developed adaptive algorithm (approximately 66% hit rate) in order to obtain comparable task difficultly across subjects. The condition (i.e., reward, punishment, neutral) of a specific trial was indicated using corresponding cues that were presented for 500 ms. After cue presentation, there was a delay (3000 ms-3500 ms) until appearance of the target stimulus. Initial duration of the target presentation was 300 ms, updated during the task according to the adaptive algorithm. In between subsequent trials, there was an intertrial interval ranging between 2500 ms and 3150 ms, following by a fixation cross (500 ms). The task consisted of five task blocks of 12 trials in pseudorandomized order. In total 60 trials (20 neutral, 20 reward, 20 punishment) were presented. Moreover, the task consisted of two rest blocks (fixation cross presentation of 10 seconds) at the start and at the end of the task. Response times and hit rates were recorded throughout the task. Subjects received an oral explanation of the task and completed a practice session before entering the MRI scanner on a laptop in the operator room to get familiar with the task. After the practice session, subjects were asked to repeat the goal of the task and cues out loud to ensure understanding of the task. During the task session inside the MRI scanner, subjects could respond using a button box in their right hand.

5.2.4 Image acquisition

Scanning was performed on a 3 Tesla SIEMENS MAGNETOM Prisma MRI scanner (Siemens, Erlangen, Germany) at the Radiology department of the UMCG. An anatomical scan (MPRAGE) was made with the following parameters; repetition time (TR) 2300 ms, echo time (TE) 2.98 ms, voxel size 1.0x1.0x1.0 mm, slice thickness 1.00 mm, flip angle 9°, field of view 256x240x176 mm. Functional multi-echo scans were made with the following parameters; TR 2170 ms, TE 9.74, 22.1 and 34.46 ms, voxel size 3.0x3.0x3.0 mm, 39 slices, slice thickness 3.00 mm, flip angle 60°, field of view 224x224 mm (Feinberg et al., 2010; Moeller et al., 2010; Xu et al., 2013).

As the design of our task was self-paced, number of volumes varied between subjects, ranging between 313 and 342 volumes.

5.2.5 Behavioral data analysis

Behavioral data were analyzed using SPSS Statistics 25 and Matlab2019a (The MathWorks Inc.,Natick, MA).

5.2.5.1 Outcome measures

Hit rates and response times were derived from the OpenSesame logfiles using an in-house developed script and used as outcome measures for task performance at the behavioral level. “Reaction time” (RT) represents the average time needed to respond to a trial of which a hit was obtained for each condition (i.e., high reward, low reward, high punishment, low punishment and neutral). “Accuracy” represents the percentage of hits for each condition.

To compute depression scores, individual MDI items were summed according to the scoring guideline and theoretically range between 0 and 50 (Bech et al., 2015). RRS-NL-EXT (trait rumination) and NEO-FFI (neuroticism) scores were computed by summing the individual items according to the scoring guidelines and theoretically range between 22 and 88 and between 12 and 60 for RRS-NL-EXT and NEO-FFI, respectively.

5.2.5.2 Statistical analysis

Differences between the task conditions across the total sample were assessed using paired sample t-tests. Differences in behavioral task performance between the trajectory groups were tested using one-way ANOVAs. When variances were found to be non-homogeneous, Welch correction was applied. Pairwise group comparisons were performed using *post-hoc* Tukey Honestly Significant Difference (HSD) tests (in case of homogeneous variances) and *post-hoc* Games Howell tests (in case of non-homogeneous variances). Behavioral task performance variables for each condition were correlated with neuroticism scores and trait rumination scores using Spearman rank correlations.

The significance level (alpha) was set to 0.05.

5.2.6 fMRI data analysis

fMRI data were analyzed using SPM12 v7487 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm) and GIFT v4.0b, implemented in Matlab2015a.

5.2.6.1 Preprocessing

First, our multi-echo functional scans were preprocessed using Multi-Echo Independent Components Analysis (ME-ICA) (Kundu, Inati, Evans, Luh, & Bandettini, 2012; Kundu et al., 2013). The ME-ICA pipeline separates the BOLD signal from non-BOLD signal using TE-dependence, calculates a T2* weighted average of the three echoes and performs several preprocessing steps, including realignment and slice-time correction. Next, we performed further preprocessing steps using SPM12; segmentation of the anatomical scan, coregistration of the functional scans to the grey matter segment of the anatomical scan and normalization (default SPM12) of all scans followed by smoothing of the functional scans with an 8 mm full-width half maximum (FWHM) Gaussian kernel.

5.2.6.2 First-level GLM

Trial onsets and durations were derived from the OpenSesame logfiles using an in-house developed script. Design matrices were specified for each subject. The following contrasts were computed at first-level:

- reward anticipation>neutral anticipation
- reward anticipation>baseline
- punishment anticipation>neutral anticipation
- punishment anticipation>baseline
- reward anticipation>punishment anticipation
- reward consumption>neutral consumption
- reward consumption>baseline
- punishment consumption>neutral consumption
- punishment consumption>baseline
- neutral consumption>baseline
- reward consumption>punishment consumption

High and low levels for both the reward condition and punishment condition were combined as one condition in the model in order to end up with a sufficient number of trials. A high pass filter of 128 seconds was applied.

5.2.6.3 Feature-based ICA

To capitalize on subject-to-subject differences and be less susceptible for lack of statistical power and unreliability issues due to small group sizes, we proceeded with independent component analysis (ICA) for our fMRI data, across our total sample. We performed three separate feature-based independent component analyses (Calhoun & Allen, 2013) on the reward anticipation>baseline, punishment anticipation>baseline and reward anticipation>punishment anticipation first-level contrast images in order to identify patterns of coactivated brain regions in response to anticipating reward

and punishment. The reward anticipation>punishment anticipation contrast was included to examine possible differences between the two experimental conditions without general task-related effects or general emotional arousal effects (Kocsel et al., 2017). The optimal number of components was estimated using the minimum description length (MDL) criterion. Independent components were estimated using the Infomax algorithm with GICA back reconstruction. Component loadings (i.e., back reconstruction values) were compared between the groups using one-way ANOVAs followed by *post-hoc* Tukey HSD tests and correlated with trait rumination and neuroticism scores using Spearman rank correlations.

The significance level (alpha) was set at 0.05.

5.3 Results

5.3.1 Characteristics trajectory groups

In previous work (Chapter 4), clustering of individual depressive symptom trajectories revealed four distinct "trajectory groups" (see Figure 1), labeled: "resilience", "fast recovery", "slow recovery" and "chronic distress". In the present chapter, we used the assigned labels to investigate a subsample (n=48) of our initial sample (n=87) that performed the fMRI MID task.

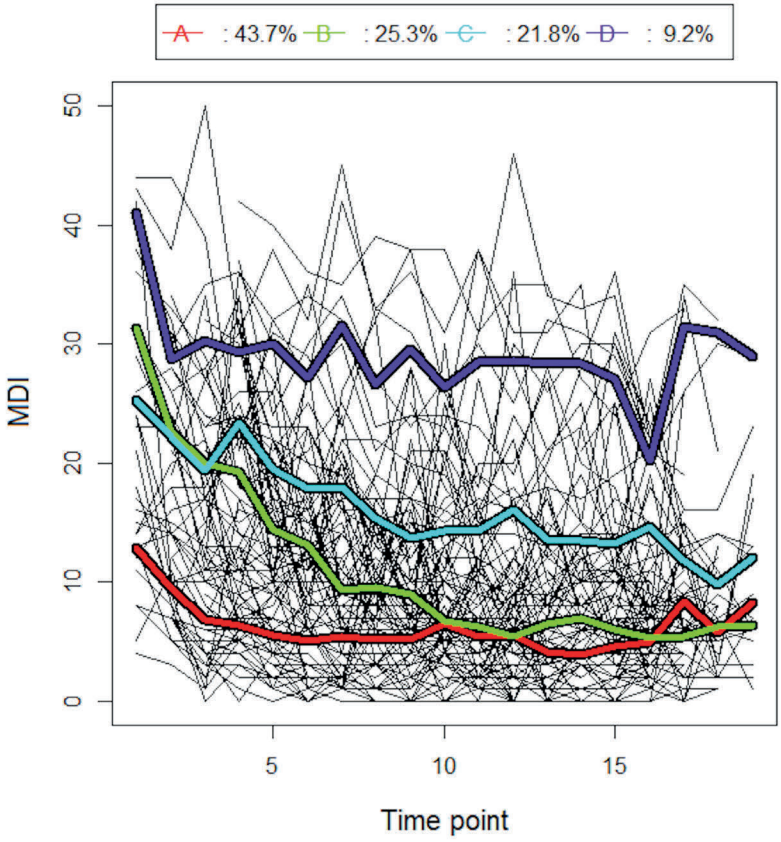

Figure 1. Initial group (*n*=87) divided into four (red=A "resilience", green=B "fast recovery", blue=C "slow recovery", purple=D "chronic distress") subgroups according to their depressive symptom trajectories (Chapter 4 of this thesis).

Characteristics of the sample included in the present chapter can be found in Supplementary Table 1. Characteristics of the trajectory groups included in the present chapter are shown in Table 1.

Table 1. Characteristics trajectory groups.

	Trajectory groups			
	Group A (*n*=19)	**Group B (*n*=13)**	**Group C (*n*=10)**	**Group D (*n*=6)**
Age	22.79±3.84	24.08±4.19	23.70±3.80	23.17±3.13
Education (%)				
high school	42.1	53.8	40.00	16.7
MBO (vocational education)	0	0	0	16.7
HBO (applied university)	5.3	23.1	40.00	33.3
university	52.6	23.1	20.00	33.3
Occupation (%)				
student	78.9	53.8	40.00	66.7
working	21.1	46.2	60.00	16.7
none of the above	0	0	0	16.7

5.3.2 Behavioral task performance

5.3.2.1 Across groups

Across groups, high reward RT ($t(47)=-3.591$, $p=0.001$), low reward RT ($t(47)=-3.335$, $p=0.002$), high loss RT ($t(47)=-5.398$, $p<0.001$) and low loss RT ($t(47)=-3.673$, $p=0.001$) were found to be significant different from neutral RT. No significant differences were found when comparing the high and low levels, both for the reward condition and punishment condition. Furthermore, reaction times of the reward condition and the punishment condition did not differ. Similar results were found for accuracy. High reward accuracy ($t(47)=5.711$, $p<0.001$), low reward accuracy ($t(47)=6.657$, $p<0.001$), high loss accuracy ($t(47)=5.283$, $p<0.001$) and low loss accuracy ($t(47)=4.376$, $p<0.001$) differed significantly from neutral accuracy.

5.3.2.2 Trajectory group differences in behavioral task performance

We used one-way ANOVA tests to examine between-group differences in behavioral task performance. The behavioral task performance per trajectory group is shown in Figure 2.

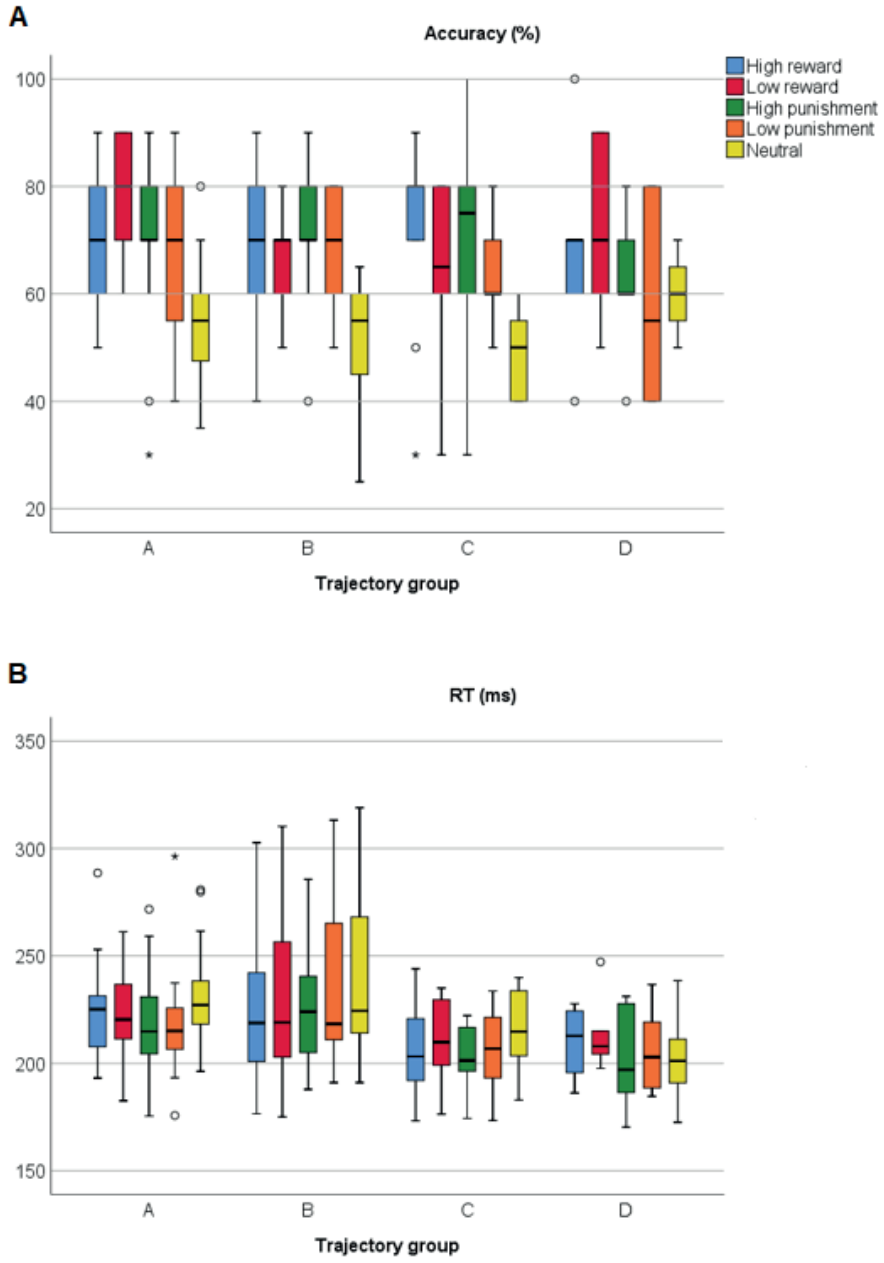

Figure 2. Behavioral task performance (A accuracy, B reaction time) for the four trajectory groups. Outliers (values that are between Q1-1.5*IQR or Q3+1.5*IQR and Q1-3*IQR or Q3+3*IQR) are indicated with a circle. Extreme outliers (values that are beyond Q1-3*IQR or Q3+3*IQR) are indicated with a star.

No group differences were observed in accuracy for any of the conditions. Between-group differences were observed in RT of the neutral condition, which remained significant after Welch's correction for non-homogeneous variances ($F(3,17.637)=3.614$, $p=0.034$). Pairwise group comparisons did not survive *post-hoc* Games-Howell tests.

5.3.2.3 Association behavioral task performance and personality traits

A significant negative correlation was found between neuroticism score and RT of the neutral condition ($r_s=-0.311$, $p=0.032$, see Figure 3).

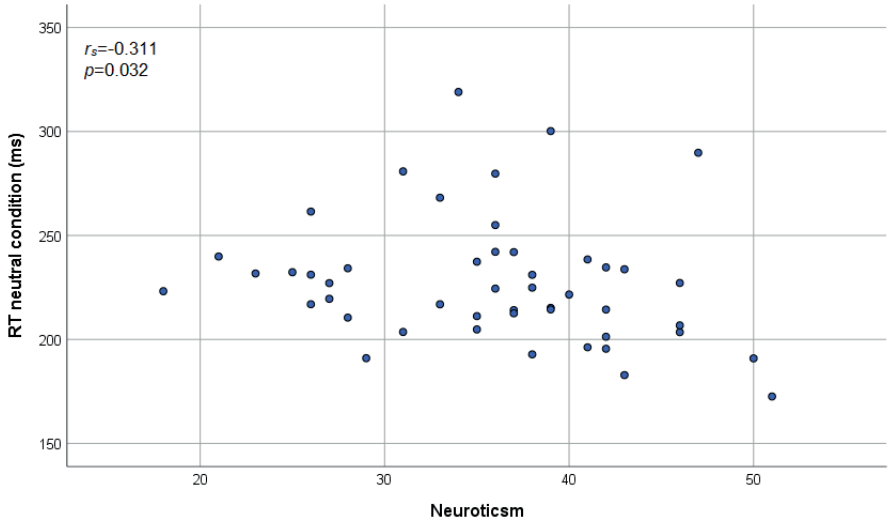

Figure 3. Relationship between neuroticism score and RT of the neutral condition.

Furthermore, a significant negative correlation was found between trait rumination score and accuracy of the low punishment condition ($r_s=-0.293$, $p=0.043$). An overview of the non-significant correlations can be found in Supplementary Table 2 and Supplementary Table 3.

5.3.3 fMRI results

5.3.3.1 Coactivated brain regions during processing of reward and punishment

Feature-based ICA estimated six components for the reward anticipation>baseline contrast (Figure 4).

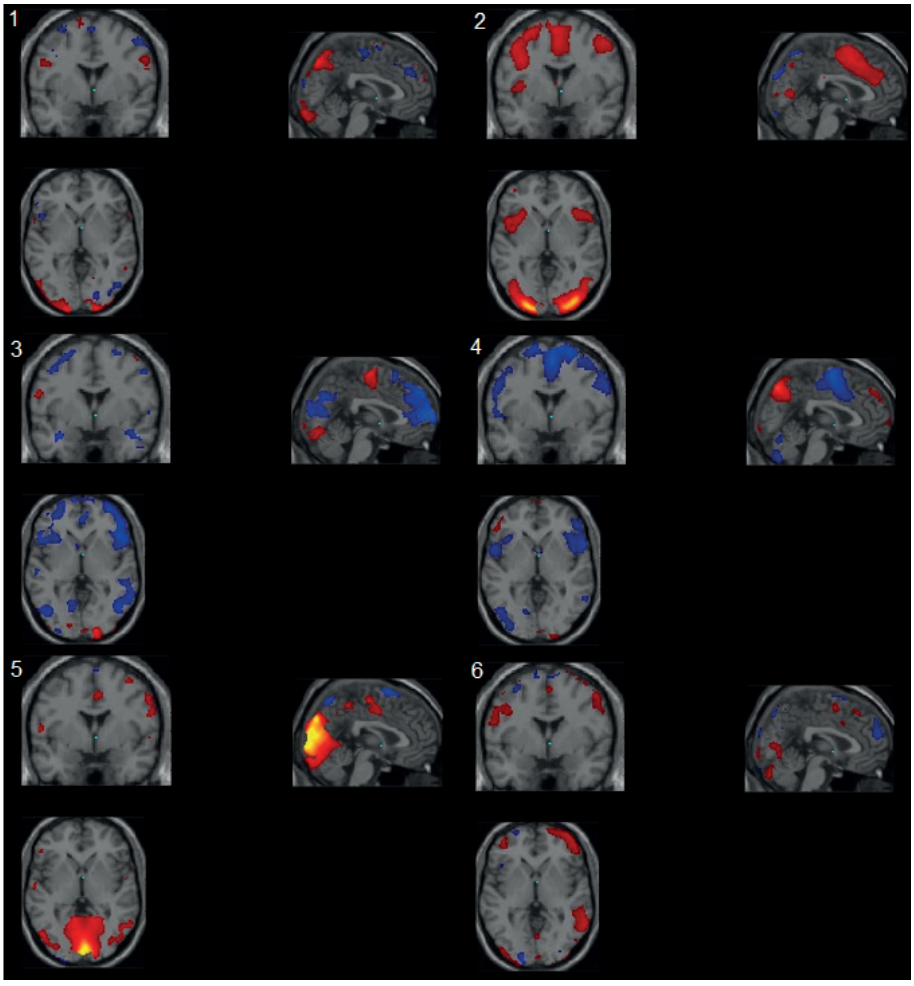

Figure 4. Estimated components for the reward anticipation>baseline contrast. Z-values above the threshold of 1.0 are displayed. Positive activation and negative activation are depicted in red and blue, respectively.

Peak coordinates and main brain regions are shown in Table 2.

Table 2. Peak coordinates and main brain regions (B=blue/negative activation, R=red/positive activation) of the estimated components for the reward anticipation>baseline contrast.

Component	Main brain regions	*Z*	MNI coordinates		
			x	***y***	***z***
1	occipital pole (R), precuneus cortex (R), paracingulate gyrus (B), superior frontal gyrus (B), middle frontal gyrus (B)	8.97	26	-92	-16
2	paracingulate gyrus (R), supplementary motor cortex (R), occipital pole (R), lateral occipital cortex (R)	6.04	-26	-94	6
3	superior frontal gyrus (B), supplementary motor cortex (R), cuneal cortex (B)	6.42	-28	-24	72
4	anterior cingulate gyrus (B), supplementary motor cortex (B), precuneus cortex (R), superior frontal gyrus (R)	8.91	-34	-70	50
5	cuneal cortex (R), lingual gyrus (R), supplementary motor cortex (R)	5.52	2	-88	16
6	superior frontal gyrus (B), frontal pole (R), lateral occipital cortex (R), middle temporal gyrus (R)	8.90	42	-54	54

For the punishment anticipation>baseline contrast, six components were estimated (Figure 5).

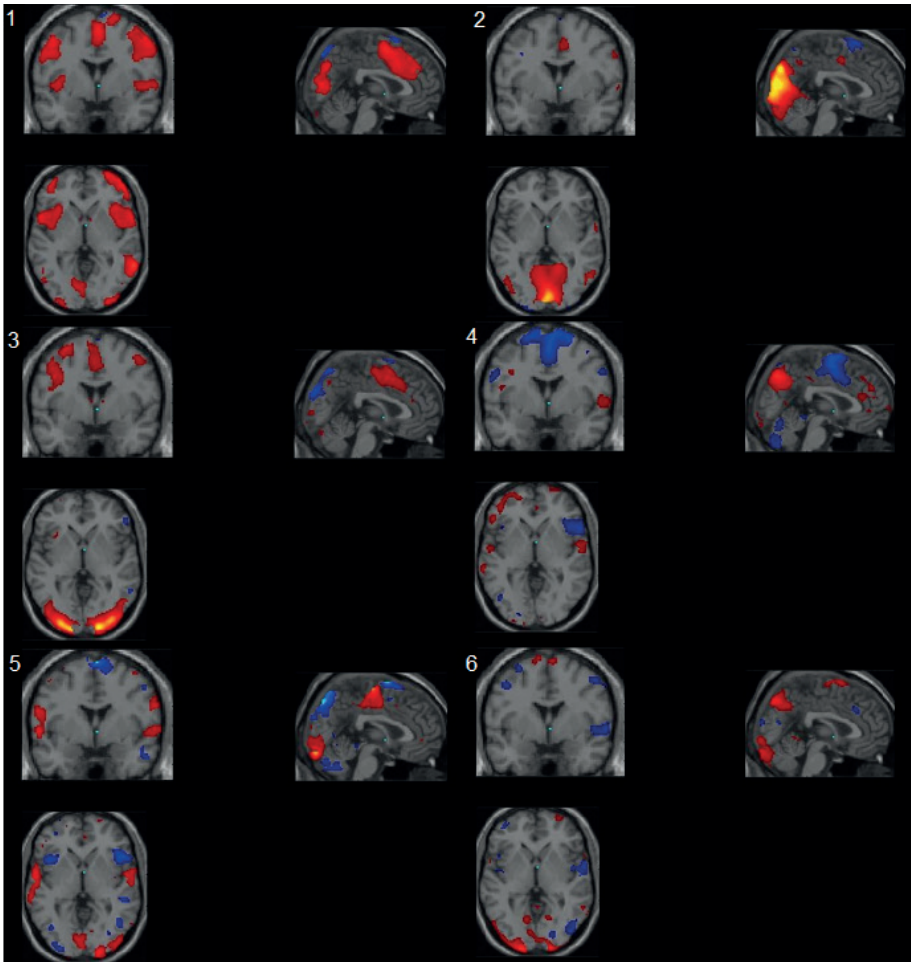

Figure 5. Estimated components for the punishment anticipation>baseline contrast. Z-values above the threshold of 1.0 are displayed. Positive activation and negative activation are depicted in red and blue, respectively.

Peak coordinates and main brain regions are shown in Table 3.

Table 3. Peak coordinates and main brain regions (B=blue/negative activation, R=red/positive activation) of the estimated components for the punishment anticipation>baseline contrast.

Component	Main brain regions	*Z*	MNI coordinates		
			x	***y***	***z***
1	anterior cingulate gyrus (R), supplementary motor cortex (R), precuneus cortex (B)	4.31	42	-52	54
2	cuneal cortex (R), lingual gyrus (R), superior frontal gyrus (B), anterior cingulate gyrus (R)	5.91	2	-86	14
3	supplementary motor cortex (R), cuneal cortex (B), occipital fusiform gyrus (R)	6.35	-26	-94	6
4	supplementary motor cortex (B), precuneus cortex (R), anterior cingulate gyrus (R)	9.61	-30	-74	48
5	supplementary motor cortex (R), precuneus cortex (B), lingual gyrus (R)	5.49	-42	-22	62
6	precuneus cortex (R), supplementary motor cortex (R), paracingulate gyrus (B), occipital fusiform gyrus (R), frontal pole (R), angular gyrus (R), superior frontal gyrus (B)	8.14	22	-90	-16

For the reward anticipation>punishment anticipation contrast, five components were estimated (Figure 6).

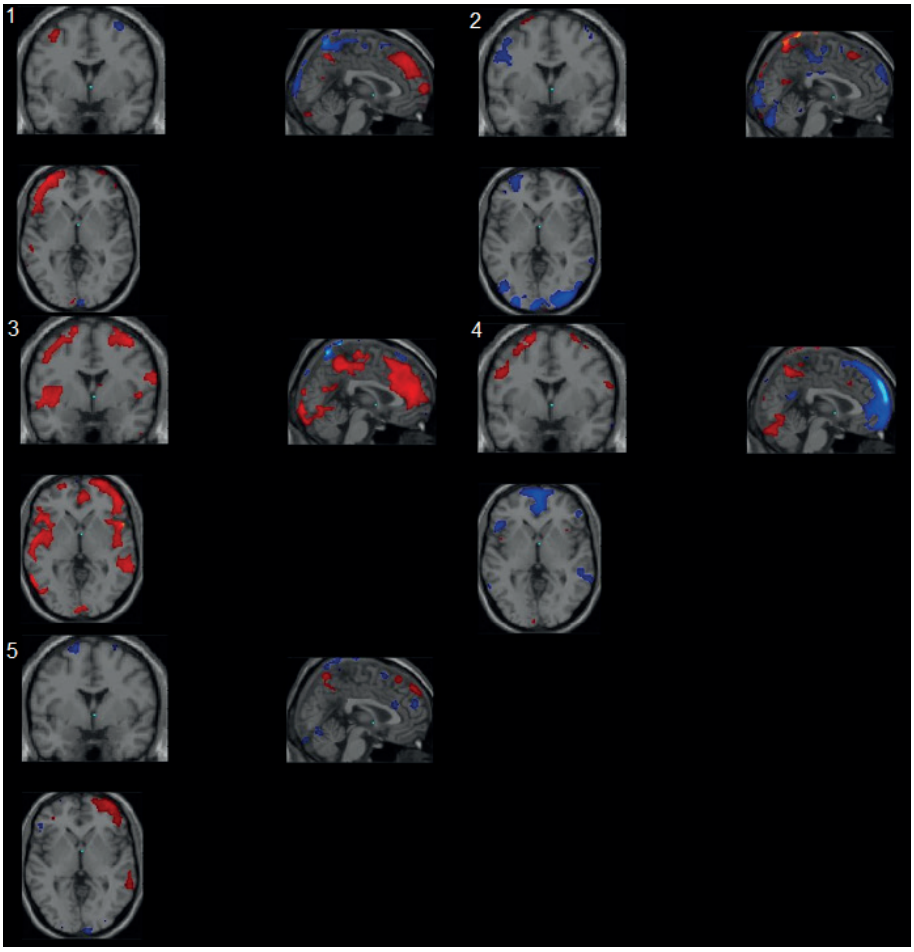

Figure 6. Estimated components for the reward anticipation>punishment anticipation contrast. Z-values above the threshold of 1.0 are displayed. Positive activation and negative activation are depicted in red and blue, respectively.

Peak coordinates and main brain regions are shown in Table 4.

Table 4. Peak coordinates and main brain regions (B=blue/negative activation, R=red/positive activation) of the estimated components for the reward anticipation>punishment anticipation contrast.

Component	Main brain regions	*Z*	MNI coordinates		
			x	***y***	***z***
1	superior frontal gyrus (R), frontal pole (R), occipital pole (B)	6.53	-30	-74	46
2	occipital pole (B), lateral occipital cortex (R), superior parietal lobule (B), frontal pole (B), superior frontal gyrus (R), precuneus cortex (R)	7.44	4	-42	80
3	paracingulate gyrus (R), precentral gyrus (R), occipital pole (R), precuneus cortex (B)	4.81	-50	16	-8
4	frontal pole (B), superior frontal gyrus (B), posterior cingulate gyrus (B), lateral occipital cortex (R), precuneus cortex (R), supramarginal gyrus (R)	5.46	-12	-74	52
5	frontal pole (R), lateral occipital cortex (R), occipital pole (B), middle frontal gyrus (R), precentral gyrus (B)	10.00	36	-66	52

5.3.3.2 Component loading differences between the trajectory groups

Significant group differences in component 4 (C4) loading were found for the reward anticipation>punishment anticipation contrast ($F(3,44)=3.26$, $p=0.030$). Pairwise *post-hoc* Tukey HSD tests revealed a significant difference between trajectory groups C and D ($p=0.040$), with higher mean loadings for group D (0.014±0.023) compared to group C (-0.007±0.013). Figure 7 displays the C4 loadings for the reward anticipation>punishment anticipation contrast per trajectory group.

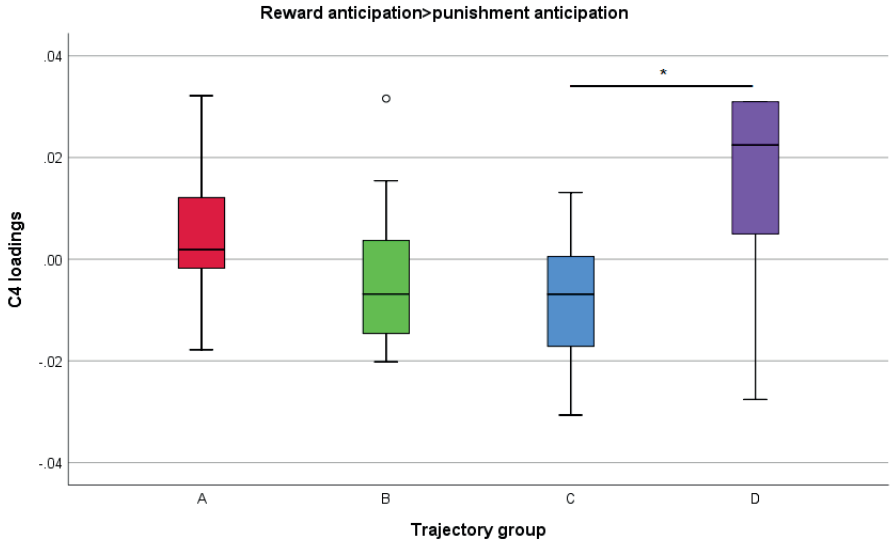

Figure 7. C4 loadings for the reward anticipation>punishment anticipation contrast per trajectory group. Outliers (values that are between Q1-1.5*IQR or Q3+1.5*IQR and Q1-3*IQR or Q3+3*IQR) are indicated with a circle.

5.3.3.3 Associations component loadings and personality traits

For the reward anticipation>baseline contrast, a significant negative correlation was found between component 1 and neuroticism score (r_s=-0.330, p=0.022). For the punishment anticipation>baseline contrast, no correlations were found between personality trait (both neuroticism and rumination) and any of the component loadings.

For the reward anticipation>punishment anticipation contrast, loadings on component 2 correlated significantly with trait rumination (r_s=-0.350, p=0.015). An overview of the non-significant correlations can be found in Supplementary Table 4, 5 and 6.

5.4 Discussion

In this chapter, we primarily investigated whether processing of reward and punishment relates to depressive symptom trajectory following romantic relationship breakup. Secondary, we investigated whether personality traits of rumination and neuroticism relate to processing of reward and punishment in our sample. To this end, women who experienced a breakup performed a variant of the MID task.

5.4.1 Behavioral task performance

At the behavioral level, we found faster reaction times and higher accuracies for the experimental conditions (reward and punishment) compared to the control (neutral) condition. This indicates that our subjects were more motivated when reward or punishment was involved. Furthermore, a between-group difference was found for reaction time of the neutral condition. However, this between-group difference did not survive *post-hoc* pairwise group comparisons. Moreover, reaction time of the neutral condition negatively correlated with neuroticism score, which indicates that individuals with higher levels of neuroticism tend to respond faster. Accordingly, we speculate that high levels of neuroticism affect the ability to switch, in terms of performing maximally, between potentially rewarding trials and control trials. Previous research already showed worse cognitive flexibility among people who are susceptible for ruminative thinking (Davis & Nolen-Hoeksema, 2000) and this style of thinking has been linked to high neuroticism (Roelofs et al., 2008). However, here we did not find a similar correlation for trait rumination.

5.4.2 Coactivated brain regions and relatedness with depressive symptom trajectory

At the neural level, we identified brain areas that coactivate during reward anticipation and punishment anticipation across our total sample. Furthermore, we identified brain regions that coactivate when contrasting reward anticipation with punishment anticipation, representing differences in brain activation between the two conditions regardless of general task-related activation or activation related to general emotional arousal. Subsequently, we investigated whether the four depressive symptom trajectory groups differ with

regard to these identified brain components. During anticipation of reward and punishment (compared to baseline), task-related brain regions were found such as visual regions and regions typically involved in executive control. In addition, some striatal activation was observed. The four groups did not differ with regard to their loadings on any of the reward anticipation>baseline or punishment anticipation>baseline components, suggesting that motivational aspects of obtaining reward or avoiding punishment at brain level are not related to affectedness and recovery after a breakup. Interestingly, when contrasting reward anticipation with punishment anticipation, one of the identified components differed between the groups. Specifically, the "chronic distress group" had higher loadings on component 4 than the "slow recovery group". This component mainly represents negative activation in frontal areas (i.e., frontal pole, superior frontal gyrus) and, to a lesser extent, positive activation in parietal and occipital areas. The frontal pole and the superior frontal gyrus play a central role in executive control functions (Bludau et al., 2016; Niendam et al., 2012). Additionally, the frontal pole is involved in reward-related decision-making and motivation (Soutschek, Kang, Ruff, Hare, & Tobler, 2018). This finding implies that this specific brain activation pattern, concerning the difference between reward and punishment, is more represented among individuals who were not capable to recover from the breakup, suggesting different decision-making and motivational processes at brain level. It should be noted that this subgroup still reported severe symptoms at the end of the study period/the time of the MRI scan, in contrast to the other subgroups (see Figure 1), and therefore this finding could be influenced by differences in current depressive state between the groups.

5.4.3 Association with personality traits

Secondary, we were interested in potential associations between brain activation patterns in response to reward/punishment and personality traits that have been linked to depression (i.e., rumination, neuroticism). A negative association was found between one of the reward anticipation>baseline components (component 1) and neuroticism score. This component mainly comprises positive activation in occipital regions (i.e., occipital pole) and parietal regions (i.e., precuneus), implying a greater response in those regions towards reward anticipation than to baseline. The occipital pole is involved in

vision processing and the precuneus subserves various processes such as mental imagery, integration of perceptual information and cue reactivity (Cavanna & Trimble, 2006; Courtney, Ghahremani, London, & Ray, 2014). The negative association with neuroticism score implies that this response is smaller in individuals with higher neuroticism levels, suggesting less engagement in the task while anticipating reward. Possibly, highly neurotic subjects were less motivated to obtain reward. This could be related to susceptivity for depression/anhedonia, as considered to be present in highly neurotic individuals in the general population (Costa & McCrae, 1980; Servaas, van der Velde et al., 2013). Moreover, we found a negative association between one of the reward anticipation>punishment anticipation components (component 2) and trait rumination score. This component mainly comprises occipital (i.e., occipital pole, lateral occipital cortex), parietal (i.e., superior parietal lobule) and frontal (i.e., frontal pole) brain regions displaying negative activation. This finding infers that individuals with higher trait rumination levels have less representation of this specific brain activation pattern, concerning the difference between reward anticipation and punishment anticipation.

5.4.4 Limitations

A possible limitation relates to uncertainty of the motivation of our subjects. First, it may be argued that our game-like version of the MID task is not sufficiently rewarding, as we paid our subjects based on their invested time and not based on their performance during the task. However, we believe that the design of the task was sufficient to activate reward-related pathways in the brain. At the beginning of the task, subjects were instructed and motivated by the researchers to perform as best as possible. Furthermore, across subjects, we were able to estimate networks of brain regions showing task-related activation, including some striatal activation. Moreover, previous studies showed that game-like reward paradigms or modifications of the MID task in which subjects could earn points or hypothetical money are able to activate reward-related brain areas (Bickel, Pitcock, Yi, & Angtuaco, 2009; Cao et al., 2019; Ivanov et al., 2012; Kätsyri, Hari, Ravaja, & Nummenmaa, 2013; Ponz et al., 2010). Second, we did not include a subjective measure of how engaged our subjects were during the task and how motivated they were to perform well. Nonetheless, we found a difference between the experimental

conditions (reward, punishment) and the control (neutral) condition in terms of behavioral performance; subjects were especially more accurate during the experimental conditions. This indicates that our subjects were motivated to perform well and end up with a large amount of (hypothetical) money.

Last, because of the COVID-19 pandemic and measures taken in the Netherlands, we ended up with a substantial lower number of MRI scans than initially planned. Consequently, classical mass-univariate group-level comparisons were less appropriate for our fMRI analysis. We proceeded with a statistical approach (i.e., feature-based ICA) which enabled us to detect coactivated brain areas by capitalizing on subject-to-subject differences, across our total sample. It would be interesting to conduct future studies with a larger sample size and directly compare separate (depressive symptom trajectory) subgroups.

5.4.5 Conclusion

We used the effect of a romantic relationship breakup as an experimental human model to study factors that may place individuals at a higher risk of developing depressive mood that persists over time. We specifically focused on the possible involvement of reward-related processing. Our findings carefully suggest that brain responses to reward anticipation and punishment anticipation do not play a role in the affectedness and recovery after a breakup. However, concerning the difference between reward anticipation and punishment anticipation, our findings tentatively point towards a relatedness of specific brain activation patterns with the persistence of depressive symptoms over time and personality traits that are considered to be risk factors for depression. Future studies with a larger sample size are necessary to validate our results and translate these findings to other (both non-clinical and clinical) populations.

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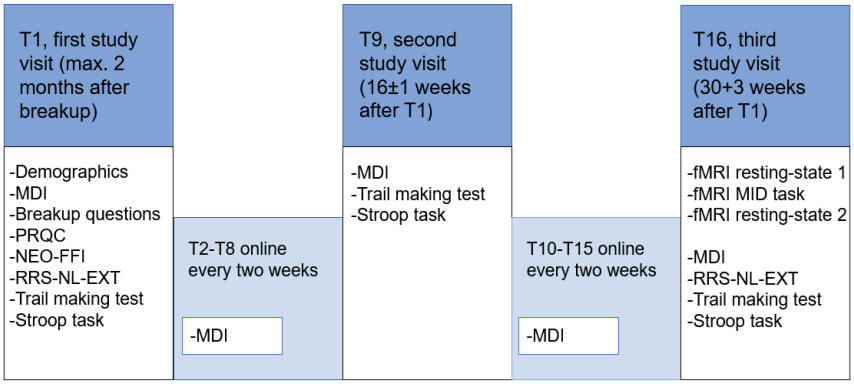
Supplementary material



Supplementary Figure 1. Overview study visits and corresponding measurements.

Supplementary Table 1. Characteristics total sample.

	Total sample (*n*=48)
Age	23.38±3.77
Education (%)	
high school	41.7
MBO (vocational education)	2.1
HBO (applied university)	20.8
university	35.4
Occupation (%)	
student	62.5
working	35.4
none of the above	2.1
NEO (neuroticism)	35.81±7.64
RRS (trait rumination)	47.04±8.16

Supplementary Table 2. Non-significant correlations behavioral task performance and neuroticism score.

Correlation	r_s	*p*
NEO-high reward accuracy	0.058	0.695
NEO-low reward accuracy	-0.162	0.270
NEO-high punishment accuracy	-0.151	0.306
NEO-low punishment accuracy	-0.161	0.274
NEO-neutral accuracy	0.090	0.545
NEO-high reward RT	-0.188	0.200
NEO-low reward RT	-0.126	0.392
NEO-high punishment RT	-0.242	0.098
NEO-low punishment RT	-0.115	0.435

Supplementary Table 3. Non-significant correlations between behavioral task performance and trait rumination score.

Correlation	r_s	*p*
RRS-high reward accuracy	0.056	0.704
RRS-low reward accuracy	-0.036	0.810
RRS-high punishment accuracy	-0.036	0.809
RRS-neutral accuracy	0.146	0.323
RRS-high reward RT	-0.102	0.490
RRS-low reward RT	-0.063	0.670
RRS-high punishment RT	-0.098	0.507
RRS-low punishment RT	-0.085	0.566
RRS-neutral RT	-0.127	0.391

Supplementary Table 4. Non-significant correlations between the component loadings for the reward anticipation>baseline contrast and personality traits.

Correlation	r_s	*p*
NEO-C2	-0.157	0.287
NEO-C3	-0.041	0.783
NEO-C4	0.277	0.057
NEO-C5	-0.154	0.296
NEO-C6	0.005	0.975
RRS-C1	-0.106	0.475
RRS-C2	0.210	0.151
RRS-C3	0.065	0.661
RRS-C4	-0.047	0.750
RRS-C5	-0.146	0.322
RRS-C6	0.098	0.509

Supplementary Table 5. Non-significant correlations between the compo-nent loadings for the punishment anticipation>baseline contrast and personality traits.

Correlation	r_s	*p*
NEO-C1	-0.254	0.082
NEO-C2	-0.131	0.374
NEO-C3	-0.083	0.576
NEO-C4	0.108	0.466
NEO-C5	0.072	0.626
NEO-C6	-0.149	0.312
RRS-C1	-0.046	0.755
RRS-C2	-0.204	0.164
RRS-C3	0.094	0.527
RRS-C4	0.017	0.910
RRS-C5	-0.169	0.252
RRS-C6	-0.102	0.491

Supplementary Table 6. Non-significant correlations between the component loadings for the reward anticipation>punishment anticipation contrast and personality traits.

Correlation	r_s	*p*
NEO-C1	0.088	0.553
NEO-C2	-0.110	0.455
NEO-C3	-0.019	0.900
NEO-C4	-0.136	0.356
NEO-C5	0.143	0.333
RRS-C1	-0.115	0.438
RRS-C3	0.025	0.867
RRS-C4	0.142	0.337
RRS-C5	0.059	0.692